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Impacts of shift work on sleep and circadian rhythms

Les impacts du travail posté sur le sommeil et les rythmes circadiens

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A B S T R A C T

Shift work comprises work schedules that extend beyond the typical "nine-to-five" workday, wherein schedules often comprise early work start, compressed work weeks with 12-hour shifts, and night work. According to recent American and European surveys, between 15 and 30% of adult workers are engaged in some type of shift work, with 19% of the European population reportedly working at least 2 hours between 22:00 and 05:00. The 2005 International Classification of Sleep Disorders estimates that a shift work sleep disorder can be found in 2–5% of workers. This disorder is characterized by excessive sleepiness and/or sleep disruption for at least one month in relation with the atypical work schedule. Individual tolerance to shift work remains a complex problem that is affected by the number of consecutive work hours and shifts, the rest periods, and the predictability of work schedules. Sleepiness usually occurs during night shifts and is maximal at the end of the night. Impaired vigilance and performance occur around times of increased sleepiness and can seriously compromise workers' health and safety. Indeed, workers suffering from a shift work sleep-wake disorder can fall asleep involuntarily at work or while driving back home after a night shift. Working on atypical shifts has important socioeconomic impacts as it leads to an increased risk of accidents, workers' impairment and danger to public safety, especially at night. The aim of the present review is to review the circadian and sleep-wake disturbances associated with shift work as well as their medical impacts.

Mots clés :
Travail posté
Travail de nuit
Rythmes circadiens
Privation de sommeil
Restriction de sommeil
Performance
Accidents
Contre-mesures

R É S U M É

Le travail posté exige des périodes de travail qui sortent du cadre conventionnel des journées "de neuf à cinq". Les horaires de travail comportent souvent un début de travail précoce, des horaires comprimés avec quarts de 12 heures ainsi que des périodes de travail de nuit. Des enquêtes récentes américaine et européenne rapportent qu'entre 15 et 30 % des travailleurs adultes travaillent sur un horaire non conventionnel, incluant 19 % de la population européenne qui rapporte travailler au moins 2 heures entre 22:00 et 05:00. La classification internationale des troubles de sommeil de 2005 estime qu'un désordre de sommeil lié au travail posté peut être observé chez 2–5 % des travailleurs. Ce désordre se caractérise par de la somnolence excessive et/ou des perturbations du sommeil pendant au moins un mois en relation avec l'horaire atypique de travail. La tolérance d'un individu au travail posté demeure un problème complexe qui dépend du nombre d'heures et de quarts consécutifs de travail, des périodes de repos et de l'aspect prévisible de l'horaire de travail. La somnolence survient généralement la nuit et est maximale en fin de nuit. Les perturbations de vigilance et de performance surviennent lors des périodes de somnolence accrue et peuvent compromettre sérieusement la santé et sécurité des travailleurs. En effet, les travailleurs souffrant du désordre de sommeil lié au travail posté peuvent s'endormir involontairement au travail et en conduisant lors du retour à domicile après un quart de nuit. Le travail posté a d'importantes implications socioéconomiques en raison du risque accru d'accidents, de

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l'altération des capacités des travailleurs et des dangers de sécurité publique qu'il comporte, en particulier la nuit. Le but du présent ouvrage est de revoir les troubles des rythmes circadiens et du cycle veille-sommeil liés au travail posté ainsi que leurs implications médicales.

1. Circadian rhythms

Near 24-hour rhythmicity regulates human physiology and behavior, and was observed in most parameters studied, such as hormone secretion [1], sleep propensity and architecture [2], and subjective and electroencephalographic (EEG)-estimated alertness [3]. The endogenous circadian nature of these rhythms is demonstrated by their persistence in the absence of external time cues and their disappearance after ablation of the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, considered the necessary master component of endogenous circadian rhythms [4].

In a subject living on a conventional day-oriented schedule, melatonin secretion starts in the evening, levels peak in the middle of the night, and slowly decline thereafter to reach their lowest levels at the end of the morning (Fig. 1). Cortisol levels also vary throughout the day. They peak at the habitual wake time and reach their nadir in the first hours of the nocturnal sleep episode. Core body temperature (CBT) varies across the circadian day. Its circadian variation is such that it reaches its nadir 1–2 hours before the regular wake time and reaches its crest 1–2 hours before the regular bedtime. Circadian phase of these rhythms is usually assessed with harmonic regression models in order to find the best fit for melatonin and cortisol peak levels, and CBT minimum. Melatonin phase can also be assessed by the so-called dim light melatonin onset (DLMO) in the evening [5].

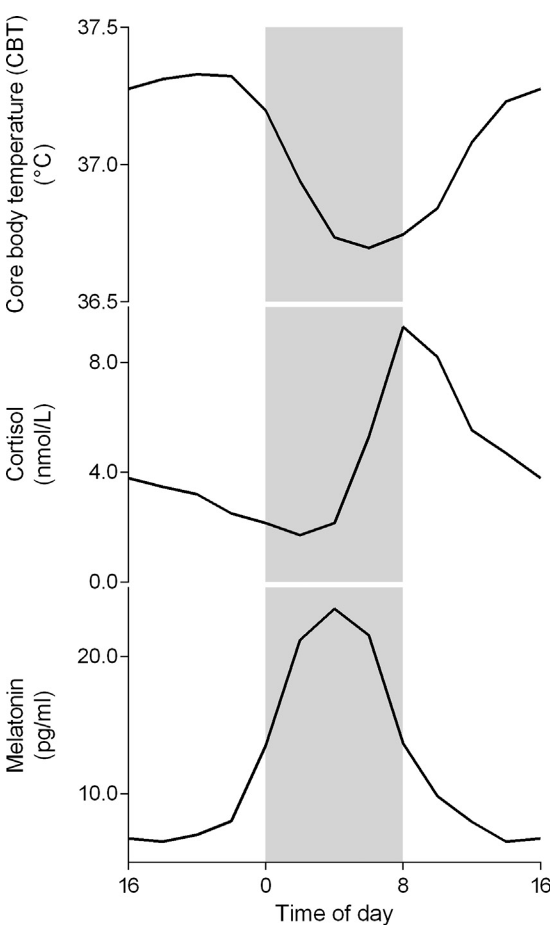

Fig. 1. Rhythms of core body temperature (CBT), cortisol and melatonin secretion in humans illustrated relative to a nocturnal sleep period (shaded area). The illustration is based on the author's data.

A set of clock genes, first identified in the SCN and later on in most tissues studied, are involved in negative and positive regulatory intracellular feedback loops, and are responsible for the generation of circadian rhythms [6]. Besides the SCN which is considered the main circadian pacemaker in mammals, cycling of clock genes were documented in various human tissues such as skin, adipose tissue, oral mucosa, peripheral blood mononuclear cells (PBMCs), bone marrow, colon cells, hair follicles, and non-SCN brain region. Oscillations generated by clock genes are thought to be transmitted to the expression of clock-controlled genes that ultimately leads to rhythms in tissue function.

In the absence of external time cues, circadian rhythms oscillate with an intrinsic period slightly different from 24 hours [7]. This endogenous period is entrained to that of the environment through daily exposure to external synchronizers, the most powerful being the light-dark cycle. The light information necessary to entrain circadian rhythms is detected by a population of specialized retinal ganglion cells containing melanopsin [8], although retinal rods and cones also play a role. Retinal light exposure is then transmitted to the SCNs via the retinohypothalamic tract, a direct and powerful monosynaptic pathway.

The light exposure schedule, its intensity, spectral composition, and the prior history of light exposure influence the size and direction of circadian phase shifts induced by light. In humans, exposure to bright light in the early morning advances circadian rhythms earlier. In contrast, exposure to bright light early at night delays these rhythms [7]. The pattern of light exposure can be planned to rapidly reset the central circadian pacemaker to earlier or later phases [9]. The central circadian clock is especially sensitive to light in the 440–480 nm spectrum such that shorter wavelength light (e.g. in the blue visible light range) can more efficiently shift the phase of the temperature and melatonin rhythms than light of longer wavelengths [10]. At lower irradiances, a switch of sensitivity towards light in the green visible spectrum of 555 nm was reported [11].

Exogenous melatonin can exert a resetting effect opposite to that of light, with evening and morning administration advancing and delaying circadian rhythms, respectively [12]. The effects of other non-photic synchronizers such as exercise, social interactions, and meal timing are less well characterized and require further experimental testing.

2. Circadian variation of sleep and waking

Sleep-wake behaviors have been shown to be regulated by a complex interaction of two processes called the homeostatic or S process, and the circadian or C process [13,14]. The homeostatic process corresponds to the build-up of sleep pressure throughout a wake period and its reduction throughout a sleep period. The S process is quantified by the amount of slow wave sleep (SWS) and slow wave activity (SWA) during non-rapid-eye movement (REM)

sleep. The S process increases with the duration of prior waking and dissipates exponentially during the sleep period. The circadian process corresponds to the oscillation of sleep propensity throughout the biological day. As wake propensity increases with the reduction of sleep propensity and vice-versa, process C also modulates the variation of wake propensity throughout the biological day.

Polysomnography (PSG)-documented sleep parameters such as sleep onset latency, sleep efficiency, REM sleep latency and duration vary with circadian phase [13]. These sleep parameters depend on the timing of sleep relative to the CBT and plasma melatonin rhythms. This circadian variation of sleep is such that, when a subject goes to bed near the CBT minimum, he falls asleep rapidly and sleeps more efficiently (Fig. 2). The reverse is seen when a subject goes to bed near the crest of the CBT cycle. This observation might be surprising as the crest and the nadir of the CBT occur in the late evening and early morning, respectively, thus, a few hours before the habitual bedtime and wake time, respectively. The special protocol

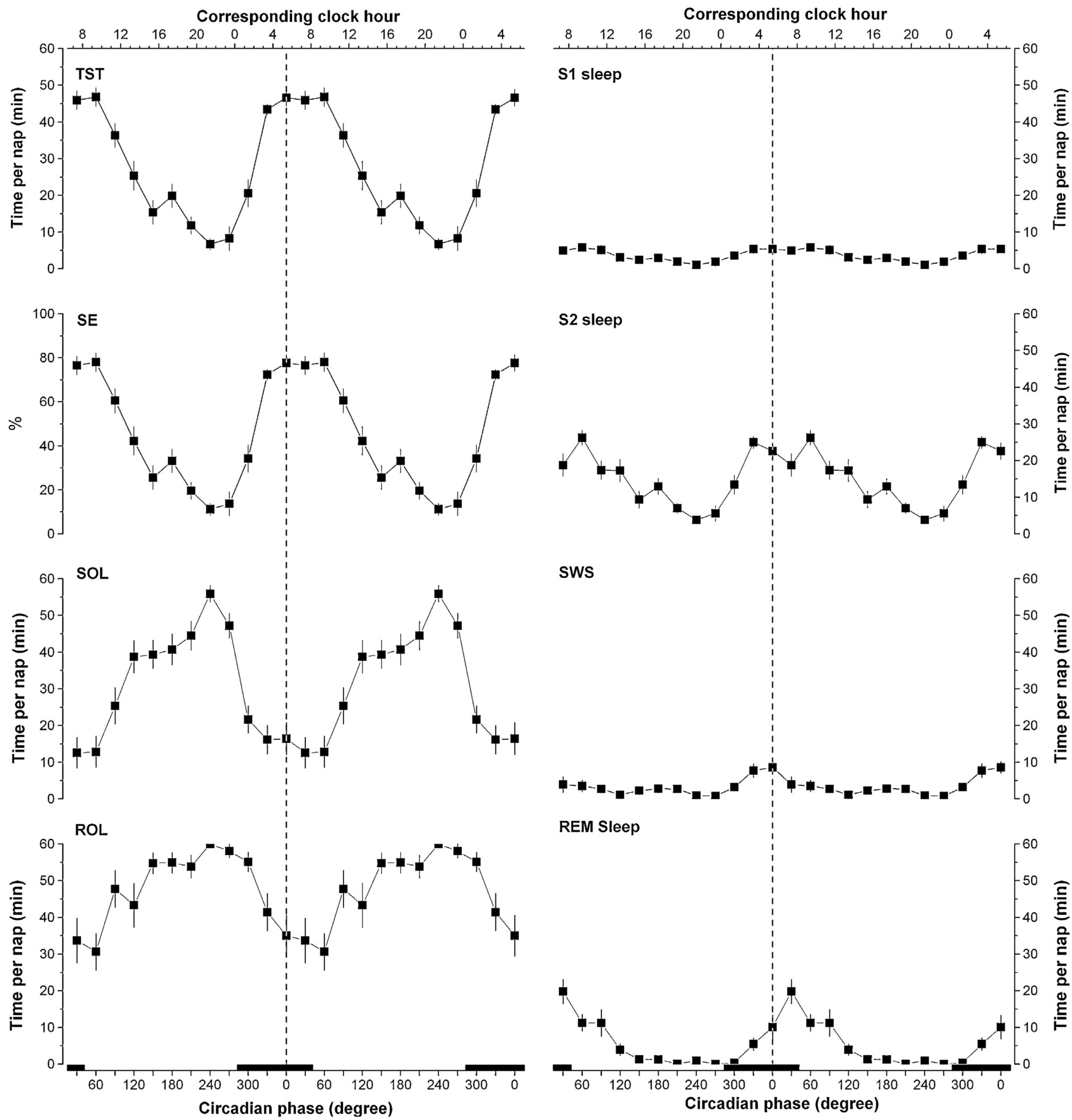

Fig. 2. Circadian variation of polysomnographic (PSG) sleep measures obtained throughout the USW procedure. This procedure consists of multiple naps planned throughout the circadian day in a condition that minimize the masking effects on the circadian system. Throughout this 48–72-hour procedure, the subject is kept in a semi-recumbent posture, with minimal activity levels, under dim light conditions. In our prior studies [2,15–18], naps are planned every 2 hours in total darkness. TST, total sleep time; SE, sleep efficiency; SOL, sleep onset latency; REMS, rapid-eye movement sleep; ROL, REMS onset latency; S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow wave sleep. All PSG measures had a significant circadian amplitude (amplitude significantly different from 0, $P < 0.05$). The vertical dotted line corresponds to the core body temperature (CBT) minimum. Bottom X axes represent circadian phase and top X axes represent the corresponding clock time (CBT minimum at 0°C = 05:23). Black bars along the X axes represent the time of projected habitual nocturnal sleep episodes. All values are means ± standard error of the mean.
Figure from Boudreau, Dumont [15].

used to assess the circadian variation of sleep propensity (such as the ultradian sleep-wake cycle procedure (USW) in Fig. 2) is designed to control for the effect of the S process. In real-life situations, both processes change throughout the day such that the S process interacts with the C process to modulate an individual's sleep-wake behavior.

A subject living on a day-oriented schedule will go to bed 1 to 2 hours after the crest of his CBT and will be able to fall asleep despite the strong circadian drive for waking because of the accumulated sleep debt during the prior wake period. In the morning, he will be able to get out of bed a few hours after his CBT nadir, thus, at the time of circadian peak propensity for sleep, because he had slept for about 8 hours the prior night.

Process C, and to some degree Process S, contribute to the appearance of two daily high sleep propensity zones [19]. One is observed at the end of the night, near the CBT minimum, and a second one occurs in the early afternoon. These two zones can explain the increased sleepiness and accidents risk in the late night as well as the post-lunch dip in alertness. Two daily low-sleep propensity zones, called "wake-maintenance zones", were also described, namely a morning one observed 3–4 hours after the regular wake time and an evening one, about 1–2 hours prior to the regular bedtime. The morning wake-maintenance zone could contribute to the sleep onset difficulties when a night shift worker goes to bed too late in the morning (anecdotal clinical report to DBB).

3. Shift work and circadian misalignment

A person working at night and sleeping during the day suffers a state of rhythms desynchrony similar to that of a traveler who flies rapidly across several time zones. Unfortunately, the entrainment of the central and peripheral clocks to a time zone change is a slow process and many days must elapse between the arrival in the new time zone and the re-entrainment of the circadian system. The circadian adaptation is more problematic for night workers who continue to be exposed to external synchronizers promoting a day-oriented schedule. As a result, many night shift workers show varying degrees of circadian adaptation to their work schedules [20] and complete adaptation in the absence of a deliberate intervention is not common in standard workplaces, as evidenced by a lack of entrainment of the CBT, melatonin, and cortisol rhythms to a night schedule [20].

In daytime workers, cortisol levels reach their minimal values early in the night and their maximal values around the regular time of awakening [21]. In comparison, melatonin levels peak at night during the middle of the sleep episode and are undetectable during the day [22]. A lack of entrainment of cortisol and melatonin rhythms to a night-oriented schedule is reported [21]. In these cases, cortisol and melatonin secretion continue to peak in the early morning hours and at night, respectively, despite the significant change in the sleep/wake schedule. Cortisol levels are significantly higher during the daytime sleep episodes of shift workers than those observed during nocturnal sleep in workers keeping a regular daytime schedule. Moreover, cortisol levels are lower during nighttime waking episodes in shift workers than during daytime waking episodes in day workers [21].

Individuals vary greatly in their degree of tolerance to shift work as it relates to the severity of circadian and sleep-wake disturbances [23]. There is evidence to suggest that circadian physiology substantially affects an individual tolerance to working shifts and factors such as gene-environment interactions [24], chronotype, phase angle of entrainment, and the daily pattern of light and darkness [15,20] are key determinants in physiological adaptation to shift work. It was reported that a complete adaptation of the circadian pacemaker to night shift work would only occur in a minority ($\leq 3\%$) of workers even if they work on a fixed night shift schedule [25]. A partial entrainment to night work would occurs in $\leq 25\%$ of this population while the majority ($\geq 72\%$) would not present any circadian adaptation [25]. However, the exact prevalence of circadian adjustment to night shift work remains controversial. Our previous study conducted among 15 patrol officers (mean $\pm$ S.D., 29.8 $\pm$ 6.5 years) shows that more than 44% of them spontaneously entrained to their night shifts [15,26]. The organization of work schedules, the sleep and light exposure behaviors of workers, their age, and health status may affect their degree of circadian entrainment to night shift work.

Our prior field study in nurses [27,28] (Fig. 3) and other laboratory [29,30] and field studies [31] indicate that timed bright light exposure can be used to promote circadian entrainment to shifted work schedules, although negative findings have been reported [32]. Stable daytime sleep schedules can also promote partial circadian entrainment as it implies regular exposure to light of intensities lower than those provided by phototherapy lamps for about 16 hours per day [33]. Dumont et al. [34] reported that 8 out of 30 night nurses presented some degree of circadian adaptation, including 5 with delayed and 3 with advanced rhythms of 6-sulfatoxy-melatonin excretion. Delayed and advanced groups of nurses differed mainly by the timing of their sleep/darkness episodes. Progressive and complete circadian adaptation occurred spontaneously throughout a week of 12-h night shifts in workers

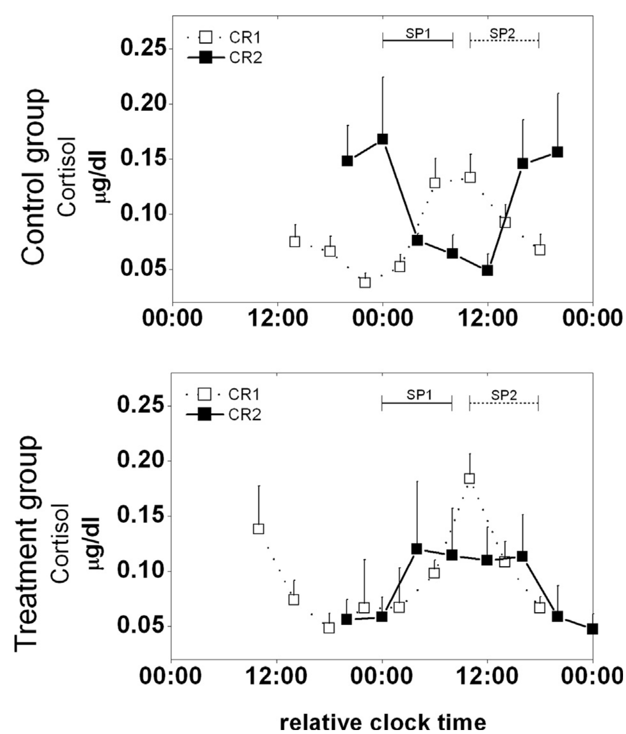

Fig. 3. Nurses were studied in a time isolation room before and after a series of 12 night shifts. Each laboratory visit comprised a 36-hour constant routine (CR) procedure designed to reliably assess circadian phase. The first CR was planned after nurses had been living at home on a day-oriented schedule for at least 10 days. The second CR was planned after their series of night shifts. There were 2 groups of nurses. The control group of nurses worked in their usual lighting conditions (upper panel). The treatment group of nurses was exposed to intermittent bright light during the first 6 hours of night shifts (lower panel). Mean salivary cortisol concentration per 4 hours is shown ($\pm$ SEM) in both groups of nurses for initial (CR1) and final (CR2) CRs. Mean cortisol concentration was averaged across groups based on hours of awakening into each CR.
Adapted from James, Walker, Boivin [28].

on North Sea Oil installations [35] and in workers in the Antarctica [36]. Similar results were observed during 3–7 simulated night shifts in laboratory [37].

The adjustment of peripheral clocks to shifted sleep-wake schedules is largely unknown. We previously conducted a simulated night shift experiment during which 5 young healthy subjects were exposed to 8 hours of bright polychromatic white light during their simulated night shifts [38]. This experiment demonstrated rapid adjustment of central clock markers such as plasma melatonin and cortisol, whereas clock genes expression in peripheral blood mononuclear cells (PBMCs) took more than a week to adapt to the shifted sleep/wake schedule. In day-active individuals, *PER1* and *PER2* clock genes expression in human PBMCs usually peaks in the morning after awakening [39]. After 8 days of exposure to an 8-h bright light stimulus at night, these clock genes expression displayed significant circadian rhythmicity, which was in a conventional relationship with the shifted sleep/wake schedule, and peaked at the end of the afternoon. This study suggests that the light/dark cycle may affect peripheral clock gene expression in humans and that circadian molecular perturbations could lead to adverse health outcomes.

4. Working hours and the sleep-wake cycle

A person sleeps better at night and performs better during the day [40]. The sleep schedule of shift workers is irregular and often abruptly displaced at unconventional circadian phases. Initiating sleep close to the temperature nadir, as is the case after a night shift when circadian adjustment has not occurred, results in abbreviated sleep length with an increased amount of wakefulness in the later part of the displaced sleep episode [7]. Night shift workers often complain of reduced sleep quality, abbreviated sleep periods, and insomnia symptoms [41,42]. One of the most frequent complaints of night shift workers is an inability to achieve adequate amounts of sleep during the day following a night shift, and this complaint is especially pronounced when starting to work shifts [43]. According to a Statistics Canada survey, 34% of shift workers report sleep onset and maintenance difficulties compared to 25% of the daytime workers [44]. A disorder called shift work sleep-wake disorder (SWSWD) has been identified in workers with severe sleepiness and insomnia related to their work schedule. In a study of more than 2500 workers aged 18–65 years, symptoms compatible with a SWSWD were observed in 32.1% of night workers, 26.1% of workers on rotating shifts, and 18% of day workers [45]. This indicates that working on atypical schedules, outside of the conventional daytime hours, leads to a substantial increase of sleepiness and sleep complaints.

Compared to day and evening shifts, working nights, whether on a fixed or rotating schedule, is associated with the most sleep disruption [46]. The evaluation by PSG sleep recordings reveals that the average daytime sleep duration is often shortened by 1–4 hours compared to nighttime sleep resulting in a need for recovery and a 8–43% increase in nocturnal sleep duration on rest days [41,47]. Data from actigraphy [47], sleep diary [45], and PSG-based studies [48] reveal that the duration of daytime sleep in night shift workers typically ranges from 4 to 7 hours. Daytime sleep episodes, which efficiencies can fall below 80%, are easily 20% shorter than nocturnal sleep episodes after day or evening shifts [49]. Daytime sleep length may be particularly short if consecutive night shifts are planned [50]. It is also common for a worker on irregular schedules to skip a night of sleep and spend more than 20 hours without sleep, especially on the first night shift of a series [51]. On rest days, longer rest periods between shifts are useful to foster longer sleep times and recovery from the weekly sleep debt [41].

The time-of-day and circadian phase at which the shift worker initiates sleep can significantly affect the duration of his main sleep episode and is a major contributor to the impaired daytime sleep duration [48]. Melatonin starts to increase in the evening, reaches a peak in the middle of the night, and slowly decreasess to reach low undetectable levels at the end of the morning. Thus, a subject active during the day and sleeping at night will sleep during his peak melatonin secretion, a situation that could contribute to nighttime sleepiness. Night shift workers will often be awake during their nocturnal melatonin peak and will go to bed at a time-of-day that is characterized by low melatonin levels.

A better alignment between the endogenous circadian system and the shifted sleep schedule was shown to promote longer sleep episodes [42]. We previously reported that an intervention consisting of a controlled pattern of exposure to light and darkness in nurses working permanent nights could significantly delay endogenous rhythms of CBT, melatonin, and cortisol [27,28]. This phase delay shift was accompanied by an increased duration of salivary melatonin secreted during the time of the projected daytime sleep episodes. In average, this led to 31-min longer daytime sleep episodes compared to those of the control group nurses [42].

Even in the absence of controlled bright light exposure at night, the maintenance of stable sleep/darkness episodes after the end of the night shift can improve the circadian alignment with the shifted sleep/wake cycle and lead to longer daytime sleep episodes [33]. This was the case for our control group nurses who maintained a stable schedule of daytime sleep/darkness and avoided nighttime naps [42]. The duration of their daytime sleep episodes, although shorter than those of the intervention group, were relatively long compared to the daytime sleep episodes of $<$ 6 hours previously reported in train drivers based on ambulatory PSG recordings [48]. Since sleep recordings were done in very different groups and conditions, it is difficult to compare our results to those of that prior study.

Interestingly, some work shift organizations can favor a pattern of light and darkness that promote circadian adaptation to night shift. A succession of simulated night shifts over a week was shown to delay the onset of salivary melatonin by 5.5 hours and promote sleep durations to levels comparable to baseline [37]. A gradual improvement of sleep quality and duration also occurred throughout a week of night work in oil-rig workers in the North Sea [52]. We recently observed a significant delay of the endogenous salivary melatonin rhythm in about than 41% of police officers working a series of 7 consecutive night shifts [15,26]. The average daytime sleep duration and efficiency in this group of officers were similar to those achieved during nighttime sleep (Fig. 4). In officers whose circadian system did not adjust to their shifted schedule, sleep duration and efficiency were significantly reduced by 40.44 ± 14.0 min and $7.2 \pm 3.2\%$ when the officers slept during the day compared to at night. A strategy based on blue-green light at night and orange-tinted goggles in the morning was also reported to increase daytime sleep by 32–34 min/day in small groups of shift workers [53].

5. Shift work and impaired vigilance

When sleep restriction accumulates over consecutive working days, large sleep deficits may cause acute or chronic fatigue and sleepiness, especially if sufficient time is not allowed for recovery. Acute sleep deprivation impairs alertness and performance levels [54]. Controlled laboratory studies have shown a decrease in psychomotor performances and subjective alertness of about 2 standard deviations (S.D.) compared to baseline levels after 17 consecutive hours awake in participants who slept an

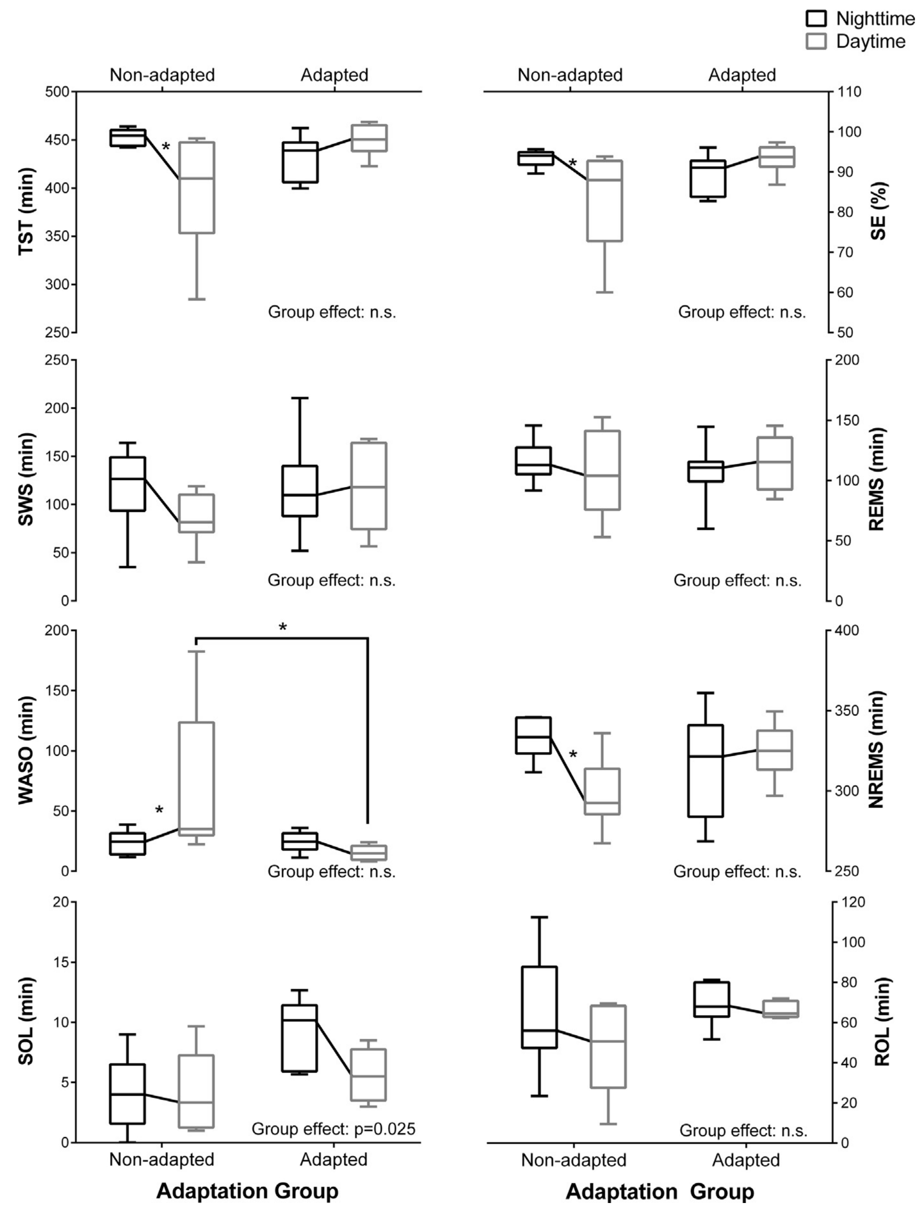

Fig. 4. Variation in the PSG sleep measurements during nighttime and daytime sleep (laboratory visits 1 and 2) in police officers working nights. The participants were considered adapted to night shift work if their salivary melatonin peaked during the daytime sleep period of their second visit. Nighttime (black boxes) and daytime (grey boxes) sleep measurements are illustrated by boxplots. The bottom and top of each box are the first and third quartiles of each group, respectively, and the band inside each box is the median. The top and bottom whiskers illustrate the 5th and 95th percentile, respectively, for each group. TST: total sleep time; SE: sleep efficiency; SWS: slow wave sleep; REMS: rapid-eye movement sleep; WASO: wake after sleep onset; NREMS: non-REM sleep; SOL: sleep onset latency; ROL: REMS onset latency. The PSG sleep measurements were compared using a linear mixed effect model with visit and adaptation group as factors. Asterisks (*) indicate a significant difference ($P < 0.05$) between laboratory visits or between groups.
Figure from Boudreau, Dumont [15].

average of 6.6 hours per day [55]. Comparable or worse levels of sleep restriction can occur in shift workers.

Chronic sleep restriction may deteriorate individuals' performances as much as acute sleep deprivation. Laboratory experiments in 48 individuals aged 21–38 years have shown that sleep restriction to 6 hours 27 minutes per day for 14 days deteriorated psychomotor performances as much as 24 consecutive hours of wakefulness [56]. Participants had to sleep 8.2 ± 3.6 hours (mean $\pm$ S.D.) per day to maintain their performances comparable to baseline throughout the study period. The long-term impacts of chronic sleep restriction on workers' health and safety are unknown. Even though shift workers often present levels of sleep restriction that are at least as severe as those seen in these studies, it remains difficult to directly extrapolate changes observed in laboratory studies to real live situations [57].

Individuals are usually very poor judges of the impact of sleep restriction on their alertness levels. A partial mismatch between subjective and objective assessments of vigilance has been previously reported with sleep curtailment [55]. When participants are restricted to 3.9 hours of sleep per day and kept awake for 20.1 consecutive hours, they will subjectively evaluate that their vigilance is reduced by about 4 S.D. compared to baseline. These data contrast with objective performance measures that show a more pronounced drop of about 5.5 S.D. [55]. This difficulty to correctly estimate the levels of performance impairment was significant at night (subjective alertness: –5.5 S.D., objective performance: –9 S.D.) and modest during the daytime.

A large variability is observed among individuals when looking at the impact of sleep deprivation on performances. The drop of

performances caused by sleep deprivation is fairly stable for an individual, but greatly varies from one individual to another. For example, the number of vigilance lapses (reaction time $\geq$ 500 ms) at the psychomotor vigilance task (PVT) observed in a group of participants after 24 hours of sleep deprivation ranged from 5 to 80 during a 10-minute session in sleep deprived subjects [56].

As it was the case for daytime sleep duration, psychomotor performances are correlated with circadian phase in night shift workers. Total or partial circadian re-entrainment by phase delay shifts can produce substantial performance improvement in night shift workers, especially in young subjects [58]. When no adjustment is achieved, a drop in alertness levels is reported in the early morning [15,42]. In our study of police officers on patrol, the officers whose peak salivary melatonin occurred during their daytime sleep period demonstrated stable performance levels throughout a series of 7 consecutive nights. In comparison, non-adapted officers whose salivary melatonin continued to peak at night had impaired alertness and performances at the end of their nights [15]. They also presented average sleep onset latencies (SOLs) of 4.24 ± 1.00 min and 4.13 ± 1.06 min when they went to bed at night and during the day, respectively. Interestingly, SOL $<$ 5 minutes corresponds to the diagnostic criteria of severe sleepiness based on the multiple sleep latency test. This observation reminds us that sleepiness occurs more frequently in night workers than in day workers [59]. Reduced performance, alertness and mood levels, as well as increased fatigue and sleepiness associated with working at night raise important safety concerns.

6. Shift work and accidents

Fatigue caused by shift work reduces cognitive performances and increases the number of attention lapses at the psychomotor vigilance task (PVT) [55]. The risk of accidents at work increases not only as a function of acute sleep deprivation, but also as a function of cumulative sleep debt [60]. The increased risk of fatigue-related accidents at work may affect all sectors in which workers are required to operate outside conventional work hours. This risk is important and under-documented in most studies because very few post-accident investigations question the worker about his lack of sleep, levels of fatigue, or his work schedule. A U.S. study found that the risk of work accidents increases by 2.77 fold during night compared to day shifts [61]. A meta-analysis of 14 recent publications indicates that shift work increases the risk of accidents at work by 50–100% [62]. According to the 2010 US National Health Survey, workers sleeping less than 6 hours per day have an 86% increased risk of accidents than those sleeping 7 to 8 hours per day [63]. Increased risk of errors and accidents among shift workers is accompanied by a 31–53% increase in absenteeism [64] and a 48–92% increase in compensations for absenteeism. It has been estimated that 11.3% of the 2.7 millions compensation claims for work accidents in Canada in 2006 was due to shift work [65]. By using the annual income dataset of Oregon, Horwitz et al. [66] have calculated the cost of additional injuries for hospital staff. They reported a 58.5% increase in accident frequency in addition to a 8.5% increased cost per claim for night workers compared to day workers.

In the healthcare sector, fatigue increases the risk of errors while reducing performances and job satisfaction [67]. Fatigue remains a major source of drug administration errors by nurses [68], which errors are 2–3 times more common among those working more than 12.5 consecutive hours [67]. The risk of fatigue-related medical errors is 7 times higher among medical residents who worked $\geq$ 5 shifts of $\geq$ 24 hours per month compared to those who worked less [69]. The same study found that fatigue is a contributing factor in 31% of accidental percutaneous punctures and increases the risk by 61% during an extended work shift [70]. This study also revealed a 35.9% increase in serious medical errors when medical residents worked on their conventional schedule compared to an improved schedule promoting rest [71]. A U.S. survey of 2737 medical residents found that the risk of car accidents and near accidents is 2.3 and 5.9 times higher, respectively, when commuting after work shifts $\geq$ 24 hours compared to shorter shifts [72].

The severity of accidents due to fatigue is particularly problematic when driving motor vehicles and for emergency teams. Studies in the transportation industry confirm that the risk of fatal accidents increases with consecutive hours of wakefulness and varies with time-of-day [73]. Sleepiness and sleep disturbances remain important factors contributing to traffic accidents [74]. For all shift workers, commuting home after long work hours or after a night shift is associated with an increased risk of motor vehicle collisions [75]. In fact, between 15 and 20% of road accidents would be caused by drivers' fatigue [76]. Sleep disturbances remain an important factor contributing to traffic accidents even in shift workers [62]. When Italian police officers were questioned about circumstances of accidents at work, while driving, or at home, they reported fatigue-related accidents twice as often (5.6% vs. 2.4%) if they worked on atypical schedules compared to daytime work [77].

7. Health risks

In addition to these safety concerns, misalignment between the sleep/wake cycle and the endogenous circadian system leads to multiple hormonal and metabolic disturbances that could negatively affect physical and mental health. When compared to day workers, shift workers have a higher risk of developing several chronic medical conditions often requiring hospitalization such as cardiovascular diseases [78], metabolic syndrome [79], gastro-intestinal diseases [78], various types of cancer [80,81], menstrual irregularities and dysmenorrhea [82], pregnancy problems [83], and psychological disorders [84]. These conditions may explain the high rates of absenteeism and long-term disability observed in shift workers [65,85].

We recently showed that an interaction between the sleep-wake and circadian processes modulates heart rate variability, and leading to altered autonomous nervous system modulation of the heart when sleep occurs at adverse circadian phases [2]. These results suggest circadian and sleep-wake dependent processes can contribute to impaired cardiovascular health in the shift workers population [78] although their role has not yet been established.

In shift workers, it was hypothesized that exposure to light at night inhibited melatonin secretion, which may increase the risk of breast cancer [86]. Recent studies have found an association between clock genes and breast cancer development in humans. Women with either the homozygous or heterozygous 5-repeat allele of *PER3* [87] or the Ala394Thr polymorphism of the *NPAS2* gene [88] seem at greater risk of breast cancer. Altogether, these data suggest that a desynchronized rhythm of clock gene expression in peripheral tissues could contribute to an increased risk of developing medical conditions.

Subjective mood varies across the 24-hour day and is also affected by a complex interaction of circadian and sleep-wake dependent processes [89]. This phenomenon may contribute to higher scores of tension-anxiety, depression, anger-hostility, fatigue and confusion reported by nurses working shifts [90].

In addition to physiological disturbances, lifestyle factors can play an important role. Compared to day workers, shift workers often eat more unhealthy food and at irregular times, with fewer meals and more snacks per day [91]. These behaviors may contribute to the increased weight gain and higher body mass

index (BMI) reported by shift workers [92]. A lack of time, motivation or energy to participate in exercise and physical fitness may also be important contributors [91].

Domestic responsibilities and housework can be substantial in female shift workers and contribute to their greater difficulty to adapt to shift work [93]. This situation can further deteriorate the quality and duration of daytime sleep, worsening the already important sleep restriction of shift working mothers.

8. Countermeasures to shift work

A number of strategies have been proposed to mitigate the symptoms associated with working shifts. Some of them are designed to promote circadian adaptation to atypical work schedules such as bright white or dimmer blue monochromatic light at night as well as neutral grey density or orange-tinted goggles during the morning commute home. Spontaneous circadian adaptation or with the help of bright light is effective to improve alertness, performances, and sleep of night shift workers [15,26]. Melatonin (0.5 mg or 3.0 mg) produced partial dose-dependent circadian phase advances and increased daytime sleep in participants who slept in the evening prior to a simulated night shift [94]. The use of 0.5 mg or 3.0 mg melatonin tablets has been proposed to produce partial dose-dependent circadian phase advances and increase daytime sleep in participants who slept in the evening prior to a simulated night shift [94]. However further large scale experimental testing is needed to support the beneficial effects of melatonin or melatoninergic receptor agonists for shift workers.

Other strategies have been proposed to maximize rest throughout the 24-hour day, such as strategic napping of 20–120 minutes in duration, hypnotics use, and the design of work rosters that maximize rest time [20]. Two types of strategic napping have been identified, namely ‘‘prophylactic naps’’ planned in the evening prior to the shift to limit anticipated sleep deprivation, and ‘‘recuperative naps’’ taken at night to temporarily relief sleepiness. Prophylactic and recuperative naps can also be considered to increase total sleep time during the day and improve alertness and performances at work [20,95]. Finally, other countermeasures have been reported to improve alertness levels during the work shift such as caffeine use, increase activity levels, and even the use of psychostimulants such as modafinil (FDA-approved to treat the SWSD) [96]. A combination therapy of 300 mg caffeine plus a 1–2 hour nap planned 3–4 hours before night shifts was shown to improve performance levels on the PVT [97]. Sleep hygiene revision [98] and cognitive behavioral therapy may also be effective in shift workers with chronic insomnia [99].

Despite their reported usefulness, most of the proposed strategies also have their limitations. Undesirable effects on the duration and/or efficiency of sleep on days off may be raised as a concern with respect to interventions designed to improve circadian adaptation to night work [52]. Issues such as the probable link between light exposure at night and cancer risk, the lack of prospective studies that carefully assess the long-term ocular safety of monochromatic blue light exposure, the uncertainty regarding the ideal naps duration, the risk of sleep inertia after awakening from a nap at night [100], and the side effects of pharmacological agents must be considered and discussed with workers. Finally, hypnotics may be considered but should be used with caution by shift workers. They can improve daytime sleep of night shift workers, but do not improve, or only modestly increase vigilance levels and nighttime performances [96]. Furthermore, short-acting hypnotic only mildly improve sleep maintenance which is the main complaint related to daytime sleep in night shift workers. As for long-acting hypnotics, they may aggravate sleepiness at work. Psychostimulants, including caffeine, should be avoided at the end of a night shift because they can interfere with daytime sleep. Despite their beneficial effects on alertness, several of the strategies proposed to acutely increase alertness levels at night are of limited utility because they temporarily mask the underlying sleep debt.

Finally, the use of sleepiness monitoring technologies at work has been proposed to prevent accidents and errors related to shift work [101]. However, these technological aids often alert workers when drowsiness is already present. These technologies should ideally be part of a comprehensive fatigue management program combining education and the use of various countermeasures to fatigue.

9. Conclusion

Working on atypical shifts has important socioeconomic impacts as it leads to an increased risk of several medical conditions in addition to increasing the risk of errors and accidents in the workplace. Important variability exists in individuals' tolerance to shift work and it is affected by several factors such as sleep-wake cycle disturbances, circadian misalignment, and predisposing individual and domestic factors. Tolerance to shift work remains a complex problem that requires a comprehensive, multilevel approach. No simple countermeasure can completely alleviate the circadian and sleep-wake disturbances shift workers present and these measures should be adapted to each individual work schedule and environment. Moreover, risks and benefits of proposed countermeasures must be carefully weighted in light of their specific limitations.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

[1] Boivin DB. Disturbances of hormonal circadian rhythms in shift workers. In: Cardinali DP, Pandi-Perumal SR, editors. Neuroendocrine correlates of sleep/wakefulness. New York: Springer; 2005. p. 325–54.

[2] Boudreau P, Yeh WH, Dumont GA, Boivin DB. Circadian variation of heart rate variability across sleep stages. Sleep 2013;36:1919–28.

[3] Van Dongen HPA, Dinges DF. Circadian rhythms in sleepiness, alertness, and performance. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia: Elsevier; 2005. p. 435–43.

[4] Silver R, Schwartz WJ. The suprachiasmatic nucleus is a functionally heterogeneous timekeeping organ. Methods Enzymol 2005;393:451–65.

[5] Ruger M, St Hilaire MA, Brainard GC, Khalsa SB, Kronauer RE, Czeisler CA, et al. Human phase response curve to a single 6.5 h pulse of short-wavelength light. J Physiol 2013;591:353–63.

[6] Cermakian N, Boivin DB. A molecular perspective of human circadian rhythm disorders. Brain Res Brain Res Rev 2003;42:204–20.

[7] Czeisler CA, Buxton OM, Khalsa SB. The human circadian timing system and sleep-wake regulation. In: Kryger M, Roth T, Dement WC, editors. Principles and practice of sleep medicine. Philadelphia: Elsevier; 2005.

[8] Hattar S, Liao HW, Takao M, Berson DM, Yau KW. Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. Science 2002;295:1065–70.

[9] Duffy JF, Wright Jr KP. Entrainment of the human circadian system by light. J Biol Rhythms 2005;20:326–38.

[10] Lockley SW, Brainard GC, Czeisler CA. High sensitivity of the human circadian melatonin rhythm to resetting by short wavelength light. J Clin Endocrinol Metab 2003;88:4502–5.

[11] Gooley JJ, Rajaratnam SM, Brainard GC, Kronauer RE, Czeisler CA, Lockley SW. Spectral responses of the human circadian system depend on the irradiance and duration of exposure to light. Sci Transl Med 2010;2:31ra3.

[12] Lewy AJ, Bauer VK, Ahmed S, Thomas KH, Cutler NL, Singer CM, et al. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. Chronobiol Int 1998;15:71–83.

[13] Dijk DJ, von Schantz M. Timing and consolidation of human sleep, wakefulness, and performance by a symphony of oscillators. J Biol Rhythms 2005;20:279–90.

[14] Borbely AA. A two process model of sleep regulation. Hum Neurobiol 1982;1:195–204.

[15] Boudreau P, Dumont GA, Boivin DB. Circadian adaptation to night shift work influences sleep, performance, mood and the autonomic modulation of the heart. PloS one 2013;8:e70813.
[16] Boudreau P, Yeh WH, Dumont GA, Boivin DB. A circadian rhythm in heart rate variability contributes to the increased cardiac sympathovagal response to awakening in the morning. Chronobiol Int 2012;29:757–68.
[17] Shechter A, Boudreau P, Varin F, Boivin DB. Predominance of distal skin temperature changes at sleep onset across menstrual and circadian phases. J Biol Rhythms 2011;26:260–70.
[18] Shechter A, Varin F, Boivin DB. Circadian variation of sleep during the follicular and luteal phases of the menstrual cycle. Sleep 2010;33:647–56.
[19] Strogatz SH, Kronauer RE, Czeisler CA. Circadian pacemaker interferes with sleep onset at specific times each day: role in insomnia. Am J Physiol 1987;253:R172–8.
[20] Boivin DB, Tremblay GM, James FO. Working on atypical schedules. Sleep Med 2007;8:578–89.
[21] Weibel L, Brandenberger G. Disturbances in hormonal profiles of night workers during their usual sleep and work times. J Biol Rhythms 1998;13:202–8.
[22] Boivin DB, James FO. Light treatment and circadian adaptation to shift work. Ind Health 2005;43:34–48.
[23] Axelsson J, Åkerstedt T, Kecklund G, Lowden A. Tolerance to shift work-how does it relate to sleep and wakefulness? Int Arch Occup Environ Health 2004;77:121–9.
[24] Gamble KL, Motsinger-Reif AA, Hida A, Borsetti HM, Servick SV, Ciarleglio CM, et al. Shift work in nurses: contribution of phenotypes and genotypes to adaptation. PloS one 2011;6:e18395.
[25] Folkard S. Do permanent night workers show circadian adjustment?. A review based on the endogenous melatonin rhythm. Chronobiol Int 2008;25:215–24.
[26] Boivin DB, Boudreau P, Tremblay GM. Phototherapy and orange-tinted goggles for night-shift adaptation of police officers on patrol. Chronobiol Int 2012;29:629–40.
[27] Boivin DB, James FO. Circadian adaptation to night-shift work by judicious light and darkness exposure. J Biol Rhythms 2002;17:556–67.
[28] James FO, Walker CD, Boivin DB. Controlled exposure to light and darkness realigns the salivary cortisol rhythm in night shift workers. Chronobiol Int 2004;21:961–72.
[29] Santhi N, Aeschbach D, Horowitz TS, Czeisler CA. The impact of sleep timing and bright light exposure on attentional impairment during night work. J Biol Rhythms 2008;23:341–52.
[30] Smith MR, Fogg LF, Eastman CI. Practical interventions to promote circadian adaptation to permanent night shift work: study 4. J Biol Rhythms 2009;24:161–72.
[31] Yoon IY, Jeong DU, Kwon KB, Kang SB, Song BG. Bright light exposure at night and light attenuation in the morning improve adaptation of night shift workers. Sleep 2002;25:351–6.
[32] Bjorvatn B, Stangenes K, Oyane N, Forberg K, Lowden A, Holsten F, et al. Randomized placebo-controlled field study of the effects of bright light and melatonin in adaptation to night work. Scand J Work Environ Health 2007;33:204–14.
[33] Santhi N, Duffy JF, Horowitz TS, Czeisler CA. Scheduling of sleep/darkness affects the circadian phase of night shift workers. Neurosci Lett 2005;384:316–20.
[34] Dumont M, Benhaberou-Brun D, Paquet J. Profile of 24-h light exposure and circadian phase of melatonin secretion in night workers. J Biol Rhythms 2001;16:502–11.
[35] Gibbs M, Hampton S, Morgan L, Arendt J. Adaptation of the circadian rhythm of 6-sulphatoxymelatonin to a shift schedule of seven nights followed by seven days in offshore oil installation workers. Neurosci Lett 2002;325:91–4.
[36] Ross JK, Arendt J, Horne J, Haston W. Night-shift work in Antarctica: sleep characteristics and bright light treatment. Physiol Behav 1995;57:1169–74.
[37] Roach GD, Lamond N, Dorrian J, Burgess H, Holmes A, Fletcher A, et al. Changes in the concentration of urinary 6-sulphatoxymelatonin during a week of simulated night work. Ind Health 2005;43:193–6.
[38] James FO, Cermakian N, Boivin DB. Circadian rhythms of melatonin, cortisol, and clock gene expression during simulated night shift work. Sleep 2007;30:1427–36.
[39] Boivin DB, James FO, Wu A, Cho-Park PF, Xiong H, Sun ZS. Circadian clock genes oscillate in human peripheral blood mononuclear cells. Blood 2003;102:4143–5.
[40] Achermann P, Borbély AA. Sleep homeostasis and models of sleep regulation. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 5th Ed., Philadelphia: Elsevier; 2011. p. 431–44.
[41] Paech GM, Jay SM, Lamond N, Roach GD, Ferguson SA. The effects of different roster schedules on sleep in miners. Appl Ergon 2010;41:600–6.
[42] Boivin DB, Boudreau P, James FO, Kin NM. Photic resetting in night-shift work: impact on nurses' sleep. Chronobiol Int 2012;29:619–28.
[43] Åkerstedt T, Nordin M, Alfredsson L, Westerholm P, Kecklund G. Sleep and sleepiness: impact of entering or leaving shiftwork – A prospective study. Chronobiol Int 2010;27:987–96.
[44] Hurst M. Qui dort la nuit de nos jour? Les habitudes de sommeil des canadiens. Statistique Canada 2008;11–008:42–8.
[45] Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. Sleep 2004;27:1453–62.
[46] Pilcher JJ, Coplen MK. Work/rest cycles in railroad operations: effects of shorter than 24-h shift work schedules and on-call schedules on sleep. Ergonomics 2000;43:573–88.
[47] Ferguson SA, Baker AA, Lamond N, Kennaway DJ, Dawson D. Sleep in a live-in mining operation: the influence of start times and restricted non-work activities. Appl Ergon 2010;82(1):71–5.
[48] Jay SM, Dawson D, Lamond N. Train drivers' sleep quality and quantity during extended relay operations. Chronobiol Int 2006;23:1241–52.
[49] Burch JB, Yost MG, Johnson W, Allen E. Melatonin, sleep, and shift work adaptation. J Occup Environ Med 2005;47:893–901.
[50] Åkerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med (Lond) 2003;53:89–94.
[51] Baulk SD, Fletcher A, Kandelaars KJ, Dawson D, Roach GD. A field study of sleep and fatigue in a regular rotating 12-h shift system. Appl Ergon 2009;40:694–8.
[52] Bjorvatn B, Stangenes K, Oyane N, Forberg K, Lowden A, Holsten F, et al. Subjective and objective measures of adaptation and readaptation to night work on an oil rig in the North Sea. Sleep 2006;29:821–9.
[53] Sasseville A, Benhaberou-Brun D, Fontaine C, Charon MC, Hébert M. Wearing blue-blockers in the morning could improve sleep of workers on a permanent night schedule: a pilot study. Chronobiol Int 2009;26:913–25.
[54] Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. Psychol Bull 2010;136:375–89.
[55] Zhou X, Ferguson SA, Matthews RW, Sargent C, Darwent D, Kennaway DJ, et al. Mismatch between subjective alertness and objective performance under sleep restriction is greatest during the biological night. J Sleep Res 2012;21:40–9.
[56] Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 2003;26:117–26.
[57] Dawson D, Ian Noy Y, Harma M, Akerstedt T, Belenky G. Modelling fatigue and the use of fatigue models in work settings. Accid Anal Prev 2011;43:549–64.
[58] Crowley SJ, Lee C, Tseng CY, Fogg LF, Eastman CI. Complete or partial circadian re-entrainment improves performance, alertness, and mood during night-shift work. Sleep 2004;27:1077–87.
[59] Gumenyuk V, Roth T, Drake CL. Circadian phase, sleepiness, and light exposure assessment in night workers with and without shift work disorder. Chronobiol Int 2012;29:928–36.
[60] Raslear TG, Hursh SR, Van Dongen HP. Predicting cognitive impairment and accident risk. Prog Brain Res 2011;190:155–67.
[61] Swanson LM, Arnedt JT, Rosekind MR, Belenky G, Balkin TJ, Drake C. Sleep disorders and work performance: findings from the 2008 National Sleep Foundation Sleep in America poll. J Sleep Res 2011;20:487–94.
[62] Wagstaff AS, Sigstad Lie JA. Shift and night work and long working hours – A systematic review of safety implications. Scand J Work Environ Health 2011;37:173–85.
[63] Lombardi DA, Wirtz A, Willetts JL, Folkard S. Independent effects of sleep duration and body mass index on the risk of a work-related injury: evidence from the US National Health Interview Survey (2004–2010). Chronobiol Int 2012;29:556–64.
[64] d'Errico A, Costa G. Socio-demographic and work-related risk factors for medium- and long-term sickness absence among Italian workers. Eur J Public Health 2012;22:683–8.
[65] Wong IS, McLeod CB, Demers PA. Shift work trends and risk of work injury among Canadian workers. Scand J Work Environ Health 2011;37:54–61.
[66] Horwitz IB, McCall BP. The impact of shift work on the risk and severity of injuries for hospital employees: an analysis using Oregon workers' compensation data. Occup Med (Lond) 2004;54:556–63.
[67] Scott LD, Rogers AE, Hwang WT, Zhang Y. Effects of critical care nurses' work hours on vigilance and patients' safety. Am J Crit Care 2006;15:30–7.
[68] Stone PW, Mooney-Kane C, Larson EL, Horan T, Glance LG, Zwanziger J, et al. Nurse working conditions and patient safety outcomes. Med Care 2007;45:571–8.
[69] Barger LK, Ayas NT, Cade BE, Cronin JW, Rosner B, Speizer FE, et al. Impact of extended-duration shifts on medical errors, adverse events, and attentional failures. PLoS Med 2006;3:e487.
[70] Ayas NT, Barger LK, Cade BE, Hashimoto DM, Rosner B, Cronin JW, et al. Extended work duration and the risk of self-reported percutaneous injuries in interns. JAMA 2006;296:1055–62.
[71] Landrigan CP, Rothschild JM, Cronin JW, Kaushal R, Burdick E, Katz JT, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. N Engl J Med 2004;351:1838–48.
[72] Barger LK, Cade BE, Ayas NT, Cronin JW, Rosner B, Speizer FE, et al. Extended work shifts and the risk of motor vehicle crashes among interns. N Engl J Med 2005;352:125–34.
[73] Boivin DB. Best practices compendium of fatigue countermeasures in transport operations: Transportation Development Center, Montreal, Qc, Canada; 2000 [Report n°: TP 13620E].
[74] Garbarino S, Nobili L, Beelke M, De Carli F, Ferrillo F. The contributing role of sleepiness in highway vehicle accidents. Sleep 2001;24:203–6.
[75] Di Milia L, Rogers NL, Akerstedt T. Sleepiness, long distance commuting and night work as predictors of driving performance. PloS One 2012;7:e45856.
[76] Gander P, Hartley L, Powell D, Cabon P, Hitchcock E, Mills A, et al. Fatigue risk management: organizational factors at the regulatory and industry/company level. Accid Anal Prev 2011;43:573–90.

[77] Garbarino S, De Carli F, Nobili L, Mascialino B, Squarcia S, Penco MA, et al. Sleepiness and sleep disorders in shift workers: a study on a group of italian police officers. Sleep 2002;25:648–53.
[78] Knutsson A. Health disorders of shift workers. Occup Med (Lond) 2003;53:103–8.
[79] Biggi N, Consonni D, Galluzzo V, Sogliani M, Costa G. Metabolic syndrome in permanent night workers. Chronobiol Int 2008;25:443–54.
[80] Davis S, Mirick DK. Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. Cancer Causes Control 2006;17:539–45.
[81] Schernhammer ES, Kroenke CH, Laden F, Hankinson SE. Night work and risk of breast cancer. Epidemiology 2006;17:108–11.
[82] Labyak S, Lava S, Turek F, Zee P. Effects of shiftwork on sleep and menstrual function in nurses. Health Care Women Int 2002;23:703–14.
[83] Zhu JL, Hjollund NH, Andersen AM, Olsen J. Shift work, job stress, and late fetal loss: the national birth cohort in Denmark. J Occup Environ Medicine 2004;46:1144–9.
[84] Shields M. Shift work and health. Health Rep 2002;13:11–33.
[85] Violanti JM, Fekedulegn D, Andrew ME, Charles LE, Hartley T, Vila B, et al. Shift work and long-term injury among police officers. Scand J Work Environ Health 2011;37:173–85.
[86] Stevens RG, Davis S, Thomas DB, Anderson LE, Wilson BW. Electric power, pineal function, and the risk of breast cancer. FASEB J 1992;6:853–60.
[87] Zhu Y, Brown HN, Zhang Y, Stevens RG, Zheng T. Period3 structural variation: a circadian biomarker associated with breast cancer in young women. Cancer Epidemiol Biomarkers Prev 2005;14:268–70.
[88] Zhu Y, Stevens RG, Leaderer D, Hoffman A, Holford T, Zhang Y, et al. Non-synonymous polymorphisms in the circadian gene NPAS2 and breast cancer risk. Breast Cancer Res Treat 2007;107(3):421–5.
[89] Boivin DB, Czeisler CA, Dijk DJ, Duffy JF, Folkard S, Minors DS, et al. Complex interaction of the sleep-wake cycle and circadian phase modulates mood in healthy subjects. Arch Gen Psychiatry 1997;54:145–52.
[90] Munakata M, Ichi S, Nunokawa T, Saito Y, Ito N, Fukudo S, et al. Influence of night shift work on psychologic state and cardiovascular and neuroendocrine responses in healthy nurses. Hypertens Res 2001;24:25–31.
[91] Persson M, Martensson J. Situations influencing habits in diet and exercise among nurses working night shift. J Nurs Manag 2006;14:414–23.
[92] Ha M, Park J. Shiftwork and metabolic risk factors of cardiovascular disease. J Occup Health 2005;47:89–95.
[93] Portela LF, Rotenberg L, Waissmann W. Self-reported health and sleep complaints among nursing personnel working under 12 h night and day shifts. Chronobiol Int 2004;21:859–70.
[94] Sharkey KM, Eastman CI. Melatonin phase shifts human circadian rhythms in a placebo-controlled simulated night-work study. Am J Physiol Regul Integr Comp Physiol 2002;282:R454–63.
[95] Fallis WM, McMillan DE, Edwards MP. Napping during night shift: practices, preferences, and perceptions of critical care and emergency department nurses. Crit Care Nurse 2011;31:e1–1.
[96] Roth T. Appropriate therapeutic selection for patients with shift work disorder. Sleep Med 2012;13:335–41.
[97] Schweitzer PK, Randazzo AC, Stone K, Erman M, Walsh JK. Laboratory and field studies of naps and caffeine as practical countermeasures for sleep-wake problems associated with night work. Sleep 2006;29:39–50.
[98] Wright Jr KP, Bogan RK, Wyatt JK. Shift work and the assessment and management of shift work disorder (SWD). Sleep Med Rev 2013;17(1):41–54.
[99] Jarnefelt H, Lagerstedt R, Kajaste S, Sallinen M, Savolainen A, Hublin C. Cognitive behavioral therapy for shift workers with chronic insomnia. Sleep Med 2012;13(10):1238–46.
[100] Takeyama H, Kubo T, Itani T. The nighttime nap strategies for improving night shift work in workplace. Ind Health 2005;43:24–9.
[101] Golz M, Sommer D, Trutschel U, Sirois B, Edwards D. Evaluation of fatigue monitoring technologies. Somnologie 2010;14:187–99.